29. The peptide-based immunotherapeutic agent of claim 28, wherein said analog peptide has the amino acid sequence of ~~SIKRVSNVI~~ SEQ ID NO. 14.

30. A method for treating or preventing allergic symptoms, the method comprising administering a peptide-based immunotherapeutic agent of claim 1 to a patient sensitive to two or more different allergens.

Remarks

Claims 1 and 3-30 are currently pending and before the Examiner for consideration. Claims 8-9 stand withdrawn from consideration. By this amendment claims 1, 3, 4, 6 and 7 have been amended, claim 2 has been canceled, and new claims 10-30 have been added.

The subject invention provides a unique and advantageous peptide based immunotherapeutic agents comprising linear multi-epitope peptides joined together and wherein said multi-epitope regions are derived from different cedar pollen allergens. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 1-7 have been rejected as being indefinite under 35 U.S.C. § 112, second paragraph. Claims 1-5 and 7 have also been rejected under 35 U.S.C. § 103 as being unpatentable over Rogers *et al.* in view of WO 94/01560 and further in view of Hashiguchi *et al.* or Komiyama *et al.*, or WO 94/11512 and Wallner *et al.*

The applicants have submitted a substitute declaration to correct the defect noted in paragraph 4 of the Office Action of October 12, 1999. The applicants have also amended the specification to list appropriate SEQ ID NOS for the sequences listed in the specification. A sequence listing is appended hereto.

The Office Action has rejected claims 1-7 under 35 U.S.C. § 112, second paragraph as being indefinite for the recitation of "substantially react with IgE antibodies" because it is unclear what degree of reactivity is acceptable. The fact that claim language, including terms of degree, may not be precise does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 731

F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. In the case of the instantly claimed invention, the specification does provide a standard for measuring the degree of reactivity with IgE antibodies. This is found on the paragraph bridging pages 31-32 wherein the degree of reactivity of various peptides with IgE antibodies of patients is disclosed and discussed. It is respectfully submitted that one of ordinary skill in the art would understand what is claimed in view of these teachings and that the specification provides the necessary standard for measuring the degree of reactivity for the claimed peptides. Withdrawal of this rejection is respectfully requested.

Turning to the disclosed and claimed invention, the claimed peptide-based immunotherapeutic agent can be shorter in length and therapeutically effective for a wider range of allergic patients, compared with the conventional peptide based agents. To provide such an agent, the present inventors first established T cell clones, each of which specifically recognizes different allergens, from peripheral lymphocytes of patients sensitive to the allergens. Overlapping peptides covering the entire primary structure of each allergen were prepared, and the reactivity of the T cell clones with the overlapping peptides were examined to identify the peptides recognized by the T cell clones. Then, the proliferation response of the T cell clones stimulated by each overlapping peptide was assessed in the presence of anti-HLA-DR, DQ and DP antibodies to identify the restriction molecules at the locus level. As a result, overlapping peptides containing T cell epitopes were found to be restricted by any of DR, DQ, and DP. The present inventors selected the T cell epitope peptides that are presented by different types of HLA class II molecules and have a high positivity index, thereby widening the range of patients who can effectively be treated. In other words, the present inventors are the first to provide a multi-epitope peptide that can be shorter in length and therapeutically effective for a wider range of allergic patients, compared with the

conventional multiepitope peptides, by selecting T cell epitope peptides that are restricted by HLA class II molecules with high appearance frequency in the population of patients and restricted by at least two molecules of HLA-DR, DQ, and DP, and by preparing a multi-epitope peptide constituted by the selected T cell epitope peptides.

Furthermore, the present inventors confirmed that one example of the multi-epitope peptides that are prepared using cry j 1 and cry j 2 are effective as peptide-based immunotherapeutics since the peptides stimulated all the peripheral lymphocyte samples from the 21 tested patients with cedar pollinosis but did not react with the IgE antibody of the patients (page 15, lines 15-19 of the instant specification).

Wallner *et al.* teach that the diversity of the human population with respect to its HLA haplotype has to be taken into account in defining clinical peptide candidates (page 305, right column, lines 32-35 to page 306, left column, lines 8-13). However, effectiveness of a multi-epitope peptide prepared based on the teachings of Wallner *et al.* would not have been obvious at the time when the claimed invention was made. It would have been necessary to confirm that peptides with different HLA haplotypes actually effective as immunotherapeutics. Indeed, as far as applicants know, no report confirming the effectiveness is available.

One of ordinary skill in the art could not have readily expected that a therapeutically effective multi-epitope peptide could be successfully obtained based on the combined teachings of the prior art references. This would be supported by the fact that no reference is available that describes the preparation of multi-epitope peptides comprising T cell epitopes that are derived from two or more different allergens, are restricted by different HLA II class molecules, have high positivity indices, and the evaluation of the therapeutic and preventive effects of the multi-epitope peptides.

Claims 1-5 and 7 have been rejected under 35 U.S.C. § 103 as being unpatentable over Rogers *et al.* in view of WO 94/01560 and further in view of Hashiguchi *et al.* or Komiyama *et al.*, or WO 94/11512 and Wallner *et al.* Applicants respectfully traverse the rejection on the following grounds. Applicants' respectfully submit that Rogers et al. fails to teach polypeptides which do not substantially react with IgE antibodies found in the sera

of
if allergic patients. As demonstrated in Figure 3 of Rogers et al. the peptide constructs 11-12-13 and 13-11-12 react, substantially, with the allergic sera containing IgE antibodies. This is contrasted with the instant invention in which all of the constructed peptides failed to substantially react with immune sera of the tested individuals (see Example 7, pages 30-32 and Figure 8). Thus, it is respectfully submitted that Rogers et al. fail to teach a critical element of the presently claimed invention, namely peptide constructs which fail to immunoreact with IgE antibodies in the sera of allergic individuals. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-5 and 7 have been rejected under 35 U.S.C. § 103 as being unpatentable over Rogers *et al.* in view of WO 94/01560 and further in view of Hashiguchi *et al.* or Komiyama *et al.*, or WO 94/11512 and Wallner *et al.* Applicants respectfully traverse the rejection on the following grounds. It is respectfully submitted that the combination of references fails to provide teaching, suggestion, or motivation to combine the references and that the currently applied obviousness rejection is the result of improper hindsight reconstruction of the presently claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In the case of the instantly claimed invention, it is submitted that the references, themselves, are devoid of any teaching, suggestion, or motivation to combine.

While Rogers *et al.* suggest that the methods and approaches taught within the reference may be applicable to the combination of multiple T cell epitopes from one or more

antigens into a single polypeptide chain (paragraph bridging pages 964-965), there is absolutely no suggestion to construct multi-epitope T-cell peptides having the currently recited properties nor is there a recognition that such peptides could be constructed.

Hashiguchi *et al.*, WO 94/01560, Komiyama *et al.*, WO 94/11512 and Wallner *et al.* fail to remedy this defect in the primary reference. According to the Office Action at pages 4-6, the secondary references have been cited to teach T-cell epitopes of cry j 1 and cry j 2 as well as the diversity of the human population with respect to its HLA haplotype. While WO 94/01560 teaches linear polypeptides of at least two cry j 1 T cell epitopes, the reference fails to teach or suggest that these linear polypeptides should be combined with T cell epitopes of cry j 2. Further, reliance upon this reference with respect to the selection of peptides on the basis of high positivity indices is unwarranted since selection of peptides on the basis of high positivity indices alone would not lead to peptides having the recited characteristics. As discussed in the specification at page 23, lines 20-23, the high positivity index alone cannot increase efficiency if the HLA class II molecules presenting the antigens are the same.

Hashiguchi *et al.*, WO 94/11512, and Komiyama *et al.* teach purified cry j 2 antigens and T-cell epitopes thereof. These references, likewise, fail to teach or suggest that T cell epitopes of cry j 2 should be joined with T cell epitopes of cry j 1 to form a multi-epitope peptide comprising T cell epitopes from these two allergens.

It is also respectfully submitted that the combination of references fails to teach, suggest, or provide any motivation to construct an immunotherapeutic peptide comprising at least two T-cell epitope peptides derived from two or more allergen molecules wherein: 1) each of said T-cell epitope peptides derived from a patient sensitive to said allergen, 2) reacts with peripheral lymphcytes from an allergy patient, 3) does not substantially react with allergen-specific IgE antibodies of the allergy patient, and 4) is restricted by at least two molecules of the HLA class II molecules of allergy patients selected from the group consisting of DP, DQ, and DR. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Because the combination of references fails to establish

any motivation to combine and because all limitations of the claim have not been met by the combination of references, it is respectfully submitted that a prima facie case of obviousness has not been made and that the rejection should, therefore, be withdrawn.

Applicants also respectfully submit that the rejection is also the result of improper hindsight reconstruction of the claimed invention. While applicants recognize that such a reconstruction of the invention is proper so long as an obviousness rejection takes into account only the knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure (In re McLaughlin, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971)), it is respectfully submitted that applicants' disclosure has been used to serve as the basis of the rejection currently of record. Combining prior art references without evidence of a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Additionally, the Court of Customs and Patent Appeals has stated, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

In the case of the presently claimed invention, it is unclear what motivation one of ordinary skill in the art would have had to apply the cited teachings without the guidance and disclosure of the presently claimed invention. There are a large number of allergens that exist in nature. These allergens range from wheat-flour allergens associated with baker's asthma (at least seventy (70) different allergens, Baur *et al.*) to allergens originating from animals (i.e., cat and dog dander) to a wide variety of pollen allergens. Pollen allergens include those originating from grasses, weeds, flowering plants, and trees. Attached for the Examiner's convenience is a listing of some of the known pollen allergens. Given the

hundreds or thousands of allergens which exist, an obviousness determination hinges on what would have motivated one of ordinary skill in the art, in the absence of the instant disclosure and claims, to pick the pollen allergens of the Japanese cedar for application to the teachings of Rogers *et al.*

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). In order to establish a case of prima facie obviousness, it is incumbent upon the Patent Office to determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g.*, *In re Ochiai*, 71 F.3d 1565, 1569-70, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); *In re Deuel*, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995)("[A] prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." (emphasis in original)); *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992; *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1991); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). *See also In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996) (discussing motivation to combine). It is respectfully submitted that the Office Action derived the required motivation to combine from the disclosure and teachings of the instant specification, not from the references applied against the claims. Accordingly, it is respectfully submitted that the obviousness rejection of record has improperly utilized the disclosure of these inventors as a blueprint for piecing together the prior art to defeat patentability and the withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks and the amendments to the claims, the applicants believe that the pending claims are now in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,322
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

FCE/la
Attachment: Petition and Fee for Extension of Time Under 37 CFR 1.136(a);
Declaration (37 CFR 1.63) and Power of Attorney; and
Amendment Transmittal Letter